111/ $600.00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#14

In re : U.S. Patent 4,264,611

Issued : April 28, 1981

To : Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung

For : 2,6-DIMETHYL-4,2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

TRANSMITTAL LETTER

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicants hereby apply for an extension of the term for the above-identified patent in accordance with 37 CFR §1.740. Applicants submit this application within the sixty-day period after the NDA approval of PLENDIL on July 25, 1991.

Enclosed please find a check in the amount of $600. to cover the fee for acting upon this application.

The Commissioner is hereby authorized to charge payment of any additional fees required under 37 CFR 1.740 and/or 37 CFR 1.20(n) associated with this communication or credit any overpayment to Deposit Account No. 23-1703. Two copies of this sheet are enclosed.

White & Case

Dated: September 11, 1991

John W. Ryan
Edward V. Filardi
Reg. No. 25,757

John W. Ryan
Reg. No. 33,771

WHITE & CASE
1155 AVENUE OF THE AMERICAS
NEW YORK, NEW YORK 10036
(212) 819-8515

120 RC 09/17/91 4264611 2 111 600.00 CK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	: U.S. Patent 4,264,611
Issued	: April 28, 1981
To	: Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung
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CERTIFICATE OF EXPRESS MAIL UNDER 37 C.F.R. 1.10

patent Term Extension

"Express Mail" Mailing Label
Number FB648429650

Date of Deposit September 11, 1991

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

DUNCAN E. MYERS
(Typed or Printed Name of Person mailing paper or fee)

Duncan E. Myers
(Signature of Person mailing paper or fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 4,264,611
Issued:	April 28, 1981
To:	Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung
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Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

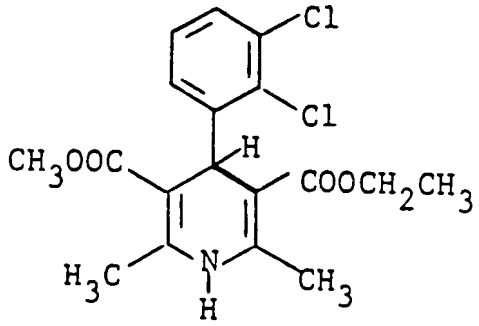
APPLICATION FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. 156

Sir:

Your Applicant, Aktiebolaget Astra, a corporation organized and existing under the laws of Sweden, whose address is S-151 85 Sodertalje, Sweden, represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. 4,264,611 granted to Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder and Bengt R. Ljung on the 28th day of April, 1981 for 2,6-DIMETHYL-4,2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME by virtue of an

assignment in favor of Aktiebolaget Hassle recorded July 7, 1982, Reel 4010 Frames 031 & 032. Your Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. 156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. 1.740). For the convenience of the Patent and Trademark Office, the information contained in this application will be presented in a format which will follow the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

(1) PLENDIL® which contains as the active ingredient, felodipine, whose chemical name is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester or ± ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate and is represented by the following structural formula:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. 355).

(3) The approved product, PLENDIL®, received permission for commercial marketing or use under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on July 25, 1991.

(4) The only active ingredient in PLENDIL® is felodipine, which has not been approved for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA 19-834 by the Food and Drug Administration on July 25, 1991.

(5) This Application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. 1.720(f), said period which will expire on September 23, 1991.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors: Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung

Patent Number: U.S. Patent 4,264,611

Issued Date: April 28, 1981

Expiration Date: April 28, 1998

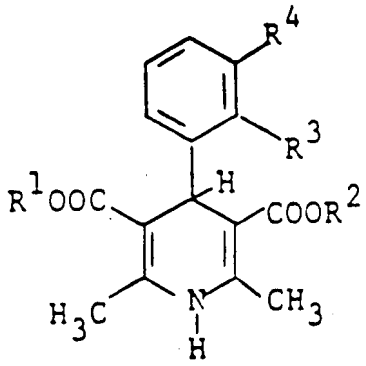
(7) See "Attachment A" for a complete copy of the patent identified in paragraph (6) hereof.

(8) No disclaimer or receipt of maintenance fee payment has been issued with regard to U.S. Patent 4,264,611. Certificate of Correction for U.S. Patent 4,264,611 was issued September 1, 1981. Reexamination Certificate B1 4,264,611 was issued on July 17, 1984. A copy of the Certificate of Correction and the Reexamination Certificate is attached hereto as "Attachment B" and "Attachment C", respectively.

(9) U.S. Patent 4,264,611 claims the approved product. Specifically, the active ingredient, felodipine, is claimed in Claims 1, 2 and 11; the pharmaceutical composition containing the active ingredient, felodipine, is claimed in claims 7, 8, 10 and 21; and the method of treatment utilizing the active ingredient, felodipine, is claimed in claims 4 and 5.

Claim 1 reads as follows:

1. A compound of the formula I



(I)

wherein R^1 is selected from the group consisting of $-CH_3$, $-C_2H_5$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, R^2 is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, $-C(CH_3)_2CH_2OCH_3$, and $-CH_2C(CH_3)=CH_2$, whereby R^1 and R^2 are not the same, R^3 is chloro and R^4 is selected from the group consisting of chloro, and methyl.

Felodipine is a compound of claim 1 wherein R^1 is $-CH_3$; R^2 is $-CH_2CH_3$; R^3 is chloro and R^4 is chloro.

Claim 2 reads as follows:

2. A compound of claim 1, wherein R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$ and R^2 is selected from the group consisting of $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, and $C(CH_3)_2CH_2OCH_3$, R^3 is chloro, and R^4 is selected from the group consisting of chloro, and methyl.

Felodipine is a compound of claim 2 wherein R^1 is $-CH_3$; R^2 is $-C_2H_5$; R^3 is chloro and R^4 is chloro.

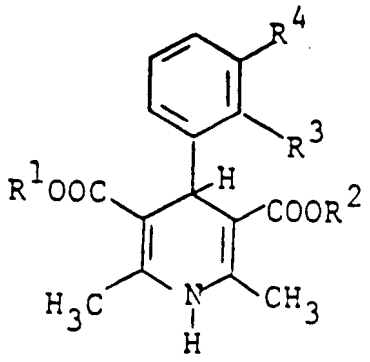
Claim 11 reads as follows:

11. The compound according to claim 1 which is 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

Felodipine is the compound of claim 11, 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

Claim 7 reads as follows:

7. Pharmaceutical preparation, which comprises as an active ingredient a therapeutically effective dose of an antihypertensive compound having vascular smooth muscle relaxing properties which compound has the formula I



(I)

wherein R^1 is selected from the group consisting of $-CH_3$, $-C_2H_5$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, R^2 is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, $-C(CH_3)_2CH_2OCH_3$, and $-CH_2C(CH_3)=CH_2$, whereby R^1 and R^2 are not the same, R^3 is chloro, and R^4 is selected from the group consisting of chloro, and methyl, in association with a pharmaceutically acceptable carrier.

The approved product is a pharmaceutical composition of claim 7 containing Felodipine which is the compound of the formula (I) wherein R^1 is $-CH_3$; R^2 is $-CH_2CH_3$; R^3 is chloro and R^4 is chloro.

Claim 8 reads as follows:

8. A pharmaceutical preparation according to claim 7, wherein the active ingredient is a compound of formula I, wherein R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, and R^2 is selected from the group consisting of $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, and $C(CH_3)_2CH_2OCH_3$, R^3 is chloro and R^4 is selected from the group consisting of chloro and methyl.

The approved product is a pharmaceutical composition of claim 8 containing Felodipine which is the compound of formula (I) wherein R^1 is $-CH_3$ R^2 is $-C_2H_5$; R^3 is chloro and R^4 is chloro.

Claim 10 reads as follows:

10. A pharmaceutical preparation according to claim 7, wherein the substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound comprises 0.1 to 99% by weight of the preparation.

The approved product in the 5 mg., 10 mg. and 20 mg. strengths contains approximately, 1 percent, 2 percent and 4 percent by weight, respectively, of a substituted 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid-diester compound which includes Felodipine.

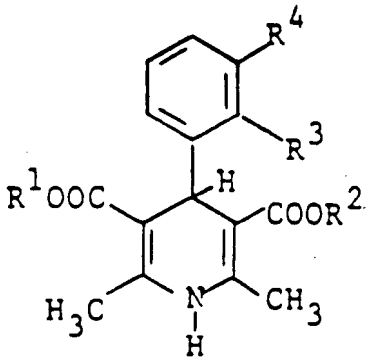
Claim 21 reads as follows:

21. A pharmaceutical preparation according to claim 7 wherein said active ingredient is the compound 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

The approved product is a pharmaceutical composition of claim 21 containing felodipine, 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-pyridine-3,5-dicarboxylic acid-3-methylester-5-ethylester.

Claim 4 reads as follows:

4. A method for treating arterial hypertension in a mammal suffering therefrom, comprising administering to said mammal an amount effective to relax the vascular smooth muscle of said mammal of a compound of formula I



(I)

wherein R^1 is selected from the group consisting of $-CH_3$, $-C_2H_5$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OCH_2H_5$, R^2 is selected from the group consisting of $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$ $-CH(CH_3)CH_2OCH_3$, $-C(CH_3)_2CH_2OCH_3$, and $-CH_2C(CH_3)=CH_2$, whereby R^1

and R^2 are not the same, R^3 is chloro, and R^4 is selected from the group consisting of chloro, and methyl.

The approved product has been indicated for the method of claim 4 utilizing Felodipine which is the compound of formula (I) wherein R^1 is $-CH_3$; R^2 is $-CH_2CH_3$; R^3 is chloro and R^4 is chloro.

Claim 5 reads as follows:

5. A method according to claim 4 wherein a compound of formula I is administered, wherein R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, and R^2 is selected from the group consisting of $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, and $C(CH_3)_2CH_2OCH_3$, R^3 is chloro and R^4 is selected from the group consisting of chloro, and methyl.

The approved product has been indicated for the method of claim 5 utilizing Felodipine which is the compound of Formula (I) wherein R^1 is $-CH_3$; R^2 is $-C_2H_5$; R^3 is chloro and R^4 is chloro.

(10) The relevant dates and information pursuant to 35 U.S.C. 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational New Drug Application (IND 24,833) for felodipine was filed on August 24, 1984 and became effective on January 16, 1986.

(ii) New Drug Application (NDA 19-834) for PLENDIL® was submitted on February 26, 1988; and

iii) New Drug Application (NDA 19-834) for PLENDIL® (felodipine) was approved on July 25, 1991.

(11) As a brief description of the activities undertaken by Applicant's Licensee, Merck & Co., Inc., during the applicable regulatory review period, attached hereto as "Attachment D" is a chronology of the major communications between the Applicant's Licensee and the FDA from August 24, 1984 and July 25, 1991.

(12) Applicant is of the opinion that U.S. Patent 4,264,611 is eligible for extension under 35 U.S.C. 156 because it satisfies all of the requirements for such extension as follows:

(a) 35 U.S.C. 156(a)

U.S. Patent 4,264,611 claims a product and a method of using a product.

(b) 35 U.S.C. 156(a)(1)

The term of the U.S. Patent 4,264,611 has not expired before submission of this application.

(c) 35 U.S.C. 156(a)(2)

The term of U.S. Patent 4,264,611 has never been extended.

(d) 35 U.S.C. 156(a)(3)

The application for extension is submitted by the owner of record in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(e) 35 U.S.C. 156(a)(4)

The product, PLENDIL®, has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. 156(a)(5)(A)

The commercial marketing or use of the product, PLENDIL®, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred.

(g) 35 U.S.C. 156(c)(4)

No other patent has been extended for the same regulatory review period for the product, PLENDIL®.

(13) The length of extension of the patent term of U.S. Patent 4,264,611 claimed by Applicant is 2.0 years or 731 days. The length of the extension was determined pursuant to 37 C.F.R. 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) began on January 16, 1986 and ended on July 25, 1991 which is a total of 2018 days or 5.52 years which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. 156(g)(2)(B)(i), the "Testing Period", began on January 16, 1986 and ended on February 26, 1988, which is 772 days or 2.11 years and

(ii) The period of review under 35 U.S.C. 156(g)(2)(B)(ii), the "Application Period", began on February 26, 1988 and ended on July 25, 1991, which is 1246 days or 3.41 years;

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph (13)(a) above (2018 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (April 28, 1981) which is 0 days, and

(ii) The number of days during which applicant did not act with due diligence which is zero (0) days, and

(iii) One-half the number of days determined in sub-paragraph (13)(a)(i) after the patent issued or 386 days which totals 1632 days;

(c) The number of days as determined in sub-paragraph (13)(b) (1632 days) when added to the original term of the patent would result in the date, October 15, 2002;

(d) Fourteen (14) years when added to the date of NDA approval (July 25, 1991) would result in the date, July 25, 2005;

(e) The earlier date as determined in sub-paragraphs (13)(c) and (13)(d) is October 15, 2002;

(f) Since both the original patent was issued before and a request for an exemption was submitted before September 24, 1984 and the commercial marketing or use of the product was not approved before September 24, 1984 two (2) years when added to the original expiration date of the patent (April 28, 1998) would result in the date, April 28, 2000;

(g) The earlier date as determined in sub-paragraph (13)(e) and (13)(f) is April 28, 2000.

Therefore, the length of extension of patent term claimed by Applicant is 731 days or 2.0 years, which is the period of time needed to extend the original expiration of term until April 28, 2000.

(14) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(15) The prescribed fee for receiving and acting upon this application is to be charged to the Deposit Account of Applicant as authorized in the attached letter, which is submitted in duplicate. The requisite declaration pursuant to rule 37 C.F.R. 1.740(b) is attached hereto.

Respectfully submitted,

Aktiebolaget Astra

By _____
Edward V. Filardi
Attorney for Applicant
Reg. No. 25,757

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.: 4,264,611

DATED: April 28, 1981

INVENTORS: Peder B. Berntsson et al.

PATENT OWNER: Aktiebolaget Astra

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

2 YEARS

with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 20th day of May 1993.

Michael K Kirk

Michael K. Kirk
Acting Commissioner of Patents and Trademarks

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	U.S. Patent 4,264,611
Issued:	April 28, 1981
To:	Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung
For:	2,6-DIMETHYL-4,2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D. C. 20231

DECLARATION

Sir:

The undersigned Attorney for Aktiebolaget Astra which is the Applicant for Extension of Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 4,264,611 hereby declares as follows:

(1) THAT he/she is a patent attorney authorized to practice before the Patent and Trademark Office and has general authority from the owner to act on behalf of the owner in patent matters;

(2) THAT he/she has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.740;

(3) THAT he/she believes the patent is subject to extension pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.710.

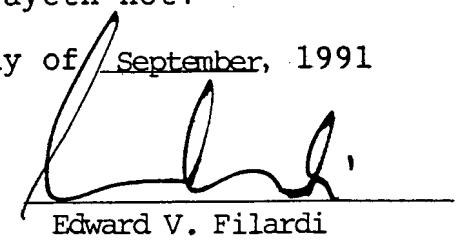
(4) THAT he/she believes an extension of the length claimed is fully justified under 35 U.S.C. 156.

(5) THAT he/she believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 C.F.R. 1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Further declarant sayeth not.

Signed this 10th day of September, 1991



Edward V. Filardi
Reg. No. 25,757

CERTIFICATION

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156 including its attachments and supporting papers is being submitted as one original and triplicate copies thereof.

John W. Ryan

Dated: September 10, 1991

United States Patent [19]
Berntsson et al.

[11] 4,264,611
[45] Apr. 28, 1981

[54] 2,6-DIMETHYL-4-2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

[75] Inventors: Peder B. Berntsson, Mölndal, Stig Å. I. Carlsson, Mölnlycke, Jan Ö. Gaarder, Göteborg, Bengt R. Ljung, all of Sweden

[73] Assignee: Aktiebolaget Hassle, Mölndal, Sweden

[21] Appl. No.: 50,083

[22] Filed: Jun. 19, 1979

[30] Foreign Application Priority Data

Jun. 30, 1978 [SE] Sweden 7807404

[51] Int. Cl.³ C07D 213/55; A61K 31/455

[52] U.S. Cl. 424/266; 546/321

[58] Field of Search 546/321; 424/266

[56] References Cited

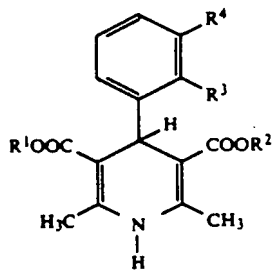
U.S. PATENT DOCUMENTS

3,441,648	4/1969	Loev et al.	546/321
3,488,359	1/1970	Bossert et al.	546/321
3,799,936	5/1974	Meyer et al.	546/321

Primary Examiner—Alan L. Rotman
Attorney, Agent, or Firm—Brumbaugh, Graves, Donohue & Raymond

[57] ABSTRACT

The present invention relates to new compounds having antihypertensive effect, which compounds are of the formula I,



(I)

wherein R^1 is selected from the group consisting of $-CH_3$, $-C_2H_5$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, and R^2 is selected from the group consisting of $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, $C(CH_3)_2CH_2OCH_3$, and $-CH_2C(CH_3)=CH_2$, whereby R^1 and R^2 are not the same, R^3 is selected from the group consisting of chloro, and R^4 is selected from the group consisting of chloro, and methyl, a method for lowering the blood pressure in mammals including man using said compounds, and pharmaceutical preparations containing said compounds.

30 Claims, No Drawings

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,264,611
DATED : April 28, 1981
INVENTOR(S) Berntsson et al.

It is certified that error appears in the above—identified patent and that said Letters Patent is hereby corrected as shown below:

First page, Item 75, after "Ljung" insert --Göteborg--;

First page, 2nd col., 6th from bottom line of ABSTRACT, after "R^3 is," delete "selected from the group consisting of";

Col. 2, line 39, ")1,4" should read --)-1,4--;

Col. 3, line 20, "(wherein" should read --wherein--;

Col. 7, line 35, "3,51" should read --3,5--;

IN THE CLAIMS:

Col. 11, lines 3 & 4, delete "and methoxy";

Col. 11, line 37, delete "$-CH(CH_3)C_2H_5$,".

Signed and Sealed this

First Day of September 1981

Attest:

Ruth M. Wray

Attesting Officer

GERALD J. MOSSINGHOFF

Commissioner of Patents and Trademarks

REEXAMINATION CERTIFICATE (221st)

United States Patent [19] [11] **B1 4,264,611**

Berntsson et al. [45] Certificate Issued **Jul. 17, 1984**

[54] **2,6-DIMETHYL-4-2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME**

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Reexamination Request:
No. 90/000,413, Jun. 30, 1983

Reexamination Certificate for:

Patent No.:	**4,264,611**
Issued:	**Apr. 28, 1981**
Appl. No.:	**50,083**
Filed:	**Jun. 19, 1979**

[30] **Foreign Application Priority Data**

Jun. 30, 1978 [SE] Sweden 7807404

[51] **Int. Cl.**[3] C07D 213/55; A61K 31/455
[52] **U.S. Cl.** 424/266; 546/321
[58] **Field of Search** 546/321; 424/266

[56] **References Cited**

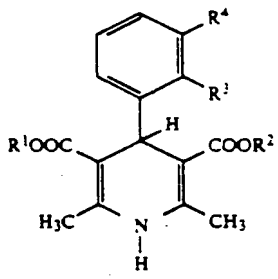
FOREIGN PATENT DOCUMENTS

2117573 10/1972 Fed. Rep. of Germany 546/321

Primary Examiner—Alan L. Rotman

[57] **ABSTRACT**

The present invention relates to new compounds having antihypertensive effect, which compounds are of the formula I,



(I)

wherein R^1 is selected from the group consisting of $-CH_3$, $-C_2H_5$, $-CH_2CH_2OCH_3$, and $-CH_2CH_2OC_2H_5$, and R^2 is selected from the group consisting of $-C_2H_5$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH(CH_3)CH_2OCH_3$, $C(CH_3)_2CH_2OCH_3$, and $-CH_2C(CH_3)=CH_2$, whereby R^1 and R^2 are not the same, R^3 is selected from the group consisting of chloro, and R^4 is selected from the group consisting of chloro, and methyl, a method for lowering the blood pressure in mammals including man using said compounds, and pharmaceutical preparations containing said compounds.

REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307.

NO AMENDMENTS HAVE BEEN MADE TO THE PATENT.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims 1-30 is confirmed.

* * * * *

Tablets PLENDIL® (Felodipine, MSD)

CHRONOLOGY OF EVENTS

IND 24,833	NDA 19-834	DATE	EVENT
X		8/24/84	IND filed for Conventional Tablets Felodipine.
X		10/9/84	FDA requested extension of 30-day waiting period to complete their review of the IND, specifically the pharmacology section and safety assessment tests.
X		10/11-26/84	Additional information is submitted to support opening of IND.
X		11/7/84	Background package for Clinical Development Meeting (End-of-Phase II Meeting in content and format) submitted.
X		12/3/84	Clinical Development Meeting held with FDA.
X		12/27/84	A summary of current studies being conducted with Felodipine by AB Hässle outside the U.S. was submitted in response to an Agency request.
X		1/14/85	Reanalysis of the mouse carcinogenicity study was submitted.
X		2/11/85	Since the FDA review of the mouse toxicology package, specifically the biometric statistical analysis, would not be complete until April, the decision was made to revise the consent form as requested by the Agency and proceed with clinical trials. The FDA approved this action and requested submission of the consent form.
X		4/4/85	Submission of draft informed consent form, revised as a result of telephone conversations with FDA. Consent form was modified to include the findings of the preclinical studies with Felodipine. The mouse carcinogenicity study was not mentioned because the statistical reanalysis submitted 1/14/85 indicated the frequency of the observation of hepatocellular tumors was not statistically significant.

IND 24,833	NDA 19-834	DATE	EVENT
X		4/25/85	Dr. C. Resnick, supervisory Pharmacologist, FDA Cardio-Renal Drug Division, reported to Dr. E. Berger that the biostatistical review of the mouse carcinogenicity study would be required before a decision could be made on the revised consent form.
X		5/29/85	In a telephone conversation with Dr. Mhatre, he reported that the FDA analysis of the mouse carcinogenicity identified some significant increases in the incidence of specific liver tumors and recommended these statements be included in the consent form. MSDRL requested the results of this review and a meeting with FDA to resolve this issue.
X		6/24/85	A background package was submitted in preparation for the FDA/MSDRL meeting concerning the mouse carcinogenicity report. Included in this package is a report by Dr. R. Squire, hired as a consultant, and additional statistical documentation.
X		7/25/85	In a meeting with Dr. Lipicky, Dr. Blois reports that in order to resolve the consent form issue, wording concerning the equivocal results of the mouse carcinogenicity would be included. Also a repeat study would be performed and this would be included.
X		8/26/85	Submission of a revised patient consent form including a paragraph on the results of the mouse carcinogenicity study under the Preclinical Safety Section.
X		9/23/85	In a conversation with Dr. C. Resnick, the FDA informed MSDRL it did not concur with the revised consent form and requests significant changes.
X		10/1/85	In accordance with Dr. Resnicks request a revised consent form was submitted.
X		10/8/85	At the joint MSDRL/FDA Meeting, approval to begin clinical trials was obtained.

IND 24,833	NDA 19-834	DATE	EVENT
X		11/21/85	FDA approval of the revised consent form (10/1/85 version) was obtained.
X		1/16/86	Dr. Lipicky approved "rearranged" consent form. Revised at the request of several investigators.
X		1/17/86	Submission of protocol 001 entitled "A Multicenter, Double-Blind, Randomized Clinical Study to Evaluate the Antihypertensive Efficacy, Safety and Tolerability of Felodipine Compared to Hydrochlorothiazide and to Placebo in Mild Essential Hypertension."
X		4/15/86	Submission of protocol 002 entitled "A Multicenter, Double-Blind, Randomized Clinical Study to Evaluate the Antihypertensive Efficacy, Safety and Tolerability of Felodipine Compared to Atenolol and to Placebo", and supportive Chemistry, Control and Manufacturing data.
X		10/21/86	Submission of protocol 003 entitled "A Multicenter, Double-Blind, Randomized Clinical Study to Determine the Dose Response Relationship and Safety in Patients with Mild to Moderate Essential Hypertension", and supportive Chemistry control and Manufacturing data.
X		4/16/87	Background package for Pre-NDA Meeting to be held 5/19/87 was submitted.
X		5/19/87	Pre-NDA Meeting held with FDA to discuss content of Felodipine ER New Drug Application based on conventional tablet data. Dr. Lipicky approved plan to file single NDA with the ER formulation.
X		6/4/87	Submission of preclinical reports: Oral Toxicity & DART Studies.
X		2/26/88	Submission of New Drug Application for Tablets SPLENDIL (Felodipine, MSD).

IND 24,833	NDA 19-834	DATE	EVENT
	X	4/19/88	As requested, submission to Dr. Bette Barton, FDA Division of Scientific Investigations, of investigator information for seventeen controlled clinical trials, including principal investigator name, address, and number of subjects.
	X	4/27/88	Mr. Warren Rumble, CSO, Cardio-Renal Drug Division, confirmed that application was filed on April 28, 1988 and due date is August 24, 1988.
	X	5/4/88	Dr. Bette Barton, selected six U.S. investigators and requested study documentation including curriculum vitae, form FDA 1572, protocols and case report forms for six patients per investigator.

Investigator Name	Protocol/Study No.
A. J. Lewin	001/06
E. B. Nelson	001/09
J. H. Pratt	002/09
R. L. Reeves	002/10
K. C. Lasseter	003/05
J. R. Sowers	003/13

	X	5/17/88	Dr. Heino Trees, was assigned as the Primary Medical Reviewer for the NDA. He contacted MSDRL to request additional desk copies of Items 4, 7 and 8 as well as sample Case Report Forms for the three U.S. trials and two Hässle E.R. trials.
	X	6/27/88	Submission of Item 9 - Safety Update Report to NDA 19-834. Data report period was from June 30, 1987 through February 29, 1988. During this period safety data on 441 new patients treated with felodipine was received increasing the total exposure to 3227.
	X	6/28/88	Submission to Dr. Bette Barton of patient enrollment data on AB Hässle clinical trials.
X		7/6/88	Submission of Oncogenicity Study in Male Mice.

IND 24,833	NDA 19-834	DATE	EVENT
	X	7/15/88	While at FDA, Dr. Berger visited Dr. Simmons and received a copy of the Chemistry Review. He reported that the application was acceptable with no major deficiencies. However, Dr. Simmons requested the tradename be changed as SPLENDIL is too "fanciful" and implies unique effectiveness.
	X	8/18/88	Letter received from Agency containing Chemistry Review comments, identical to draft received on 7/18/88.
	X	8/23/88	Dr. J. Vick, Pharmacology/Toxicology reviewer, reported his review was complete and no major deficiencies were noted.
	X	9/6/88	Dr. Simmons contacted regarding his review comments and use of ASTRA manufacturing facilities. The issue of an overseas inspection was raised.
X		9/30/88	An Investigational New Drug Application was filed for the Extended Release formulation of Felodipine. All future clinical studies will be conducted under IND 32,184 using this formulation. This IND contained generic protocols 004 and 005 which would study the use of Felodipine in Elderly and Young patients and those with Isolated Systolic Hypertension respectively.
	X	10/4/88	Submission of responses to Chemistry, Manufacturing and Controls issues contained in 8/18/88 letter.
X		10/18/88	Submission of protocol 006 entitled "A Multicenter, Double-Blind, Randomized Clinical Study to Evaluate the Dose Response Curve and Safety of Extended-Release Felodipine in Patients with Mild to Moderate Hypertension."
	X	11/10/88	Dr. H. Trees was contacted on status of his review. He was finished and would recommend approval of application to Dr. Lipicky.

IND 32,184	NDA 19-834	DATE	EVENT
	X	12/8/88	Submission of outline of all manufacturing and packaging facilities as requested by Dr. Simmons. Also revised stability summary and update on Stability Data in NDA. New Tradename Tablets PLENDIL officially adopted and used.
	X	1/6/89	Dr. L. DeWitt, reviewing Pharmacologist contacted concerning her review. At this time no major concerns were noted.
X		1/19/89	Submission of Protocol 007 entitled "A Double-Blind, Randomized, Parallel, Placebo-Controlled Pilot Study to Evaluate the Effects of Felodipine ER in Patients with Ischemic Cardiomyopathy and Heart Failure Concomitantly Receiving Enalapril, Diuretic and/or Digoxin."
	X	3/29/89	Mr. Rumble, CSO, reported that Dr. Ng had been assigned to do the statistical review but had not started yet. No Biopharmaceutics reviewer had been identified.
	X	4/28/89	Additional Chemistry, Manufacturing and Control comments were received.
	X	5/1/89	Mr. Rumble contacted MSDRL regarding revised labeling under DESCRIPTION and Mechanism of Action. Dr. L. DeWitt, Reviewing Pharmacologist, did not feel the NDA supported the statements describing felodipine as a calcium antagonist.
	X	6/12/89	Dr. Berger met with Drs. Simmons and Wolters regarding bioequivalence issues. MSDRL proposed performing a study comparing Astra manufactured tablets with Merck manufactured tablets from one of the three sites and providing in vitro dissolution data on the remaining sites.
	X	6/27/89	Submission of summary information and additional publications on the mechanism of action of felodipine, at Dr. DeWitt's request.

IND 32,184	NDA 19-834	DATE	EVENT
	X	7/11/89	Submission of additional responses to Chemistry review and updated Methods Validation Package to reflect use of HPLC method.
	X	7/13/89	Dr. Lipicky approved development of Summary Basis of Approval (SBOA) outline.
	X	8/1/89	Dr. L. DeWitt contacted MSDRL concerning mechanism of action of felodipine. She requested additional test methodology information.
X		8/4/89	Submission of Agenda and list of issues for 8/16/89 MSDRL/FDA meeting held to discuss Felodipine Heart Failure Program. Also, a draft outline of Summary Basis of Approval (SBOA) was included for Hypertension NDA.
	X	9/25/89	Dr. DeWitt contacted MSDRL to request two additional Pharmacology Studies to resolve the mechanism of action question.
	X	9/26/89	Submission of revised draft package circular changing tradename throughout to PLENDIL and revising CLINICAL PHARMACOLOGY section in response to Dr. DeWitt's comments.
	X	10/2/89	Dr. H. Trees contacted MSDRL with comments on the 9/26/89 draft labeling.
	X	10/17/89	Submission of proposal for *in vivo* and *in vitro* studies to support the manufacturing of PLENDIL at Merck facilities, based on discussion with FDA. Dr. T. Ng, Biometrics Division requested additional information on MSDRL studies for his statistical review.
	X	10/18/89	Dr. J. Simmons, Chemist, contacted MSDRL to request submission of samples to FDA Laboratories for validation.
	X	10/23/89	Submission of information requested by Dr. Ng including allocation schedule for Protocol 001 and information on where to locate analyses in Item 8.

IND 32,184	NDA 19-834	DATE	EVENT
	X	10/31/89	Submission of in vitro study results to document the calcium entry blocking activity of felodipine as requested by Dr. DeWitt.
	X	11/1/89	Submission of revised draft package circular, as requested by Dr. H. Trees, with responses to his issues/concerns.
X		11/9/89	Submission of Protocol 008 entitled "A Double-Blind, Two Period Crossover Study in Healthy Volunteers to Compare the Bioequivalence of the MPMD 10 mg ER Felodipine Tablet versus the Astra Manufactured 10 mg Felodipine Tablet."
	X	11/22/89	Dr. T. Ng contacted MSDRL for additional information to support his review of the statistical section of the NDA.
	X	11/27/89	Dr. L. DeWitt requested a meeting with MSDRL to resolve the mechanism of action issues.
	X	12/14/89	Dr. J. Simmons, Chemist, provided remaining Chemistry concerns, specifically requesting additional chromatographic methodology.
	X	12/21/89	Submission of responses to Dr. T. Ng's comments and additional summary statistics and efficacy analyses.
	X	1/16/90	MSDRL contacted Mr. Warren Rumble, CSO, concerning the recently completed ER Dose Response Study (Protocol 006). The study report will be submitted without data tabulations or case report forms at this time. Revised labeling reflecting the updated Adverse Reactions from this study was also discussed.
	X	1/18/90	Submission of background package for a meeting on 2/1/90 to resolve mechanism of action issues.
	X	2/1/90	MSDRL/FDA Meeting held. Dr. Lipicky stated no additional experimentation is required to demonstrate the calcium channel blocking effect of felodipine and accepted MSDRL wording on mechanism of action.

IND 32,184	NDA 19-834	DATE	EVENT
	X	2/13/90	Submission of Clinical Study Report for Protocol 006 MSDRL Dose Response Study of ER formulation and revised package circular reflecting experience obtained from this study.
	X	2/15/90	Submission of a report on the potency of various calcium antagonists on the relaxation of depolarized rat aortic smooth muscle rings, as requested by Dr. DeWitt at 2/1/90 meeting.
	X	2/20/90	MSDRL was informed that the secondary medical reviewer had been assigned to the PLENDIL NDA, Dr. A. Karkowsky. Also data tabulations and case report forms were requested for Protocol 006 MSDRL ER Dose Response Study. Receipt of FDA letter stating that the 2/13/90 submission of the findings from the dose response study was a major amendment and the FDA will restart 180 day clock. The revised due date is August 14, 1990.
	X	2/26/90	Submission of method validation samples, batch analysis, and dissolution data to FDA Laboratories in St. Louis, MO and Philadelphia, PA.
	X	2/26/90	Submission of supplemental information for inclusion in the Methods Validation Package.
	X	3/1/90	Dr. T. Ng, Biometrics Division, contacted MSDRL for additional statistical information.
	X	3/6/90	Mr. W. Rumble, CSO, requested information to assist Dr. Teng of the Biopharmaceutics Division in her review.
	X	3/15/90	Dr. T. Ng requested additional statistical analysis on all MSDRL Studies (Protocol 1, 2, 3 and 6) using the "All Patients Treated Last Value Approach".
	X	3/16/90	Submission of Data Tabulations and Case Report Forms for patients who discontinued due to adverse experience in MSDRL ER Dose Response Study (Protocol 006).

IND 32,184	NDA 19-834	DATE	EVENT
	X	3/21/90	Submission of revised HPLC Method for Assay of Felodipine Degradate.
	X	3/26/90	In accordance with the 3/6/90 request from Dr. Teng individual patient demographic and plasma concentration data for ten bioavailability studies in the NDA were submitted.
	X	3/29/90	Submission of revised draft labelling components in accordance with requests from Dr. J. Simmons, Chemist, and Dr. DeWitt, Pharmacologist.
	X	4/4/90	Submission of additional analysis as requested on 3/15/90 by Dr. Ng. A diskette was also provided.
	X	4/25/90	Submission of Clinical Study Report for Protocol 008, a Bioavailability Study comparing Merck and Astra Manufactured Tablet and comparative in vitro stability data from two proposed Merck manufacturing facilities.
	X	5/7/90	Dr. Teng requested additional biopharmaceutics data.
	X	5/31/90	Submission of additional patient data and analyses to Dr. Teng.
	X	6/1/90	Submission of background package for meeting on 6/6/90 to discuss Summary Basis of Approval (SBOA) and pre-Approval Safety Update Report.
	X	6/6/90	Meeting held with FDA, outline established for SBOA.
X		6/18/90	Submission of protocol 010 entitled "An Open Label, Multicenter Study to Evaluate the 24-Hour, Hemodynamic Effects and Plasma Drug Levels Following a Single Dose of Felodipine ER in Patients with Heart Failure."
	X	7/5/90	Mr. Gary Buehler, newly assigned CSO, contacted Dr. Berger to inform him of FDA decision to audit the rat carcinogenicity study. He requested a diskette containing all study data.

IND 32,184	NDA 19-834	DATE	EVENT
	X	11/30/90	Drs. Trees and Karkowsky requested additional data on formulations and adverse experiences as well as synopses of eleven additional ER clinical trials conducted by AB Hässle.
	X	12/12/90	Dr. Karkowsky contacted MSDRL with concerns about the bioequivalence of the 20 mg tablet, as well as additional requests for information and an interest in the effect of felodipine on bone.
	X	1/8/91	Dr. Karkowsky contacted MSDRL for additional adverse experience information by formulation and age. Later, he requested overall AEs by percentage.
	X	1/17/91	Submission of responses to Dr. Karkowsky's recent requests dealing with the safety profile of felodipine.
	X	1/31/91	Submission of responses to Dr. Karkowsky's request for additional tabulations of safety data.
	X	2/4/91	Dr. Karkowsky requested information dealing with the 8/3/90 Summary Basis of Approval and 8/29/90 Safety Update Report. These questions reflected Dr. Lipicky's comments on the medical review document.
	X	3/4/91	Submission of point-by-point response to the fourteen comments concerning the SBOA and SUR.
	X	3/25/91	Submission of two "typical" cases of edema and headache which resulted in discontinuation of felodipine treatment, as requested by Dr. Karkowsky.
	X	4/4/91	FDA informed MSDRL of pending site inspection of West Point, PA facility.
	X	4/16/91	Mr. D. Roeder informed MSDRL that an action package including an approvable letter had been circulated to all primary FDA reviewers. He also requested revised draft labeling.

IND 32,184	NDA 19-834	DATE	EVENT
	X	7/26/90	Dr. J. Simmons, Chemist, requested that the labeling for Felodipine reflect that it is a racemic mixture.
	X	8/3/90	Submission of draft Summary Basis of Approval (SBOA).
	X	8/15/90	Dr. Karkowsky requested information regarding the first dose effects of ER dosage form.
	X	8/27/90	Dr. Trees requested information of Phase III and Market Image formulations.
	X	8/29/90	Submission of diskettes containing rat carcinogenicity data as requested by FDA on 7/6/90. Submission of second Safety Update Report, from report period February 29, 1988 through May 31, 1990. The focus of this report was on ER formulation only. A total of 1382 patients had now received Tablets PLENDIL.
	X	9/5/90	Submission of Item 2, SBOA and Clinical Study Report for Protocol 006 to Mr. D. Roeder, CSO, assigned to PLENDIL NDA.
	X	9/11/90	Submission of additional information for SBOA to reflect 8/29/90 Safety Update experience.
	X	11/5/90	Submission of revised list of facilities to manufacture drug substance and drug products and alternate packaging sites.
	X	11/15/90	Submission of diskettes requested by Dr. Chi on 10/29/90, containing key efficacy and safety data from study V-606 and Protocol 006.
	X	11/19/90	Dr. Karkowsky requested breakdown of adverse experiences by dose and age as well as by formulation. Also, Dr. Simmons requested formulation clarification.

IND 32,184	NDA 19-834		DATE	EVENT
	X		4/17/91	Submission of letter withdrawing AB Astra as a manufacturing site of Tablets PLENDIL, due to backlog of site inspections by FDA.
	X		4/18/90	Dr. Karkowsky requested a pre-approval Safety Update Report, dealing only with Deaths and Discontinued Due to Adverse Experience for ER Clinical Trials and overseas serious adverse experiences.
	X		4/24/91	Submission of revised assay for felodipine, as requested by Dr. Simmons.
	X		5/3/91	Submission of draft package circular, revised to incorporate comments received from FDA on 4/19/91 and 4/25/91.
	X		5/17/91	Submission of report on the use of felodipine with ACE inhibitors to support labeling statements.
	X		5/24/91	Submission of pre-approval Safety Update Report covering report period May 31, 1990 through March 31, 1991.
	X		6/11/91	In response to requrests made by Dr. R. Wolters, as a result of the preapproval inspection, additional Chemistry Control and Manufacturing data is submitted.
		X	6/18/91	Additional labeling comments from Drs. Lipicky and Temple were recieved. Secitons concerning vascular selectivity and concomitant use with ACE inhibitors approved by FDA. Additional revisions are required before issuance of approvable letter.
		X	7/8/91	Approvable letter recieved. Additional changes in labeling were requested by FDA.
		X	7/9/91	Additional samples submitted as per request of Agency to confirm color.
		X	7/10/91	Additional page of Summary Basis of Approval (SBOA) submitted relating AE's by dose of PLENDIL monotherapy.

IND 32,184	NDA 19-834		DATE	EVENT
		X	7/17/91	Counter proposal made for PLENDIL labeling to include AE by dose table (for most common AE's). Proposal rejected by Drs. Karkowsky, Lipicky and Temple.
		X	7/18/91	Final Printed Labeling submitted incorporating Agency and MSDRL Comments.
		X	7/25/91	Approval letter issued. Market package requested.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re	:	U.S. Patent 4,264,611
Issued	:	April 28, 1981
To	:	Peder B. Berntsson, Stig A.I. Carlsson, Jan O. Gaarder & Bengt R. Ljung
For	:	2,6-DIMETHYL-4,2,3-DISUBSTITUTED PHENYL-1,4-DIHYDRO-PYRIDINE-3,5-DICARBOXYLIC ACID-3,5-ASYMMETRIC DIESTERS HAVING HYPOTENSIVE PROPERTIES, AS WELL AS METHOD FOR TREATING HYPERTENSIVE CONDITIONS AND PHARMACEUTICAL PREPARATIONS CONTAINING SAME

TRANSMITTAL LETTER

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicants hereby apply for an extension of the term for the above-identified patent in accordance with 37 CFR §1.740. Applicants submit this application within the sixty-day period after the NDA approval of PLENDIL on July 25, 1991.

Enclosed please find a check in the amount of $600. to cover the fee for acting upon this application.

The Commissioner is hereby authorized to charge payment of any additional fees required under 37 CFR 1.740 and/or 37 CFR 1.20(n) associated with this communication or credit any overpayment to Deposit Account No. 23-1703. Two copies of this sheet are enclosed.

White & Case

Dated: September 11, 1991

John W. Ryan
Edward V. Filardi
Reg. No. 25,757

John W. Ryan
Reg. No. 33,771

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